

INTERNATIONAL SEARCH REPORT

 International Application No
PCT/EP2004/014170
A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, Sequence Search**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL 'Online! 6 October 2000 (2000-10-06), "1M0228A10F Mouse 10kb plasmid UUGC1M library Mus musculus genomic clone UUGC1M0228A10 F, DNA sequence." XP002324932 retrieved from EBI accession no. EM_PRO:AZ438069 Database accession no. AZ438069 abstract	17, 18
Y	WO 02/059347 A (THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE) 1 August 2002 (2002-08-01) page 3, paragraph 3 claims 1-44 ----- -/--	1-4, 6-22

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

9 May 2005

Date of mailing of the international search report

22 09. 2005

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Tudor, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/38801 A (HUMAN GENETIC SIGNATURES PTY LTD; GRIGG, GEOFFREY, WALTER; MOLLOY, PET) 16 May 2002 (2002-05-16) claims 1,2,4,8,12-14,16,17 -----	1-4,6-22
Y	MARTIN V ET AL: "Genomic sequencing indicates a correlation between DNA hypomethylation in the 5' region of the pS2 gene and its expression in human breast cancer cell lines" GENE, ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, NL, vol. 157, no. 1, 19 May 1995 (1995-05-19), pages 261-264, XP004042334 ISSN: 0378-1119 abstract page 261, left-hand column, paragraph 1 - right-hand column, line 4 page 262, right-hand column, paragraph 2-4 -----	1-4,6-22
Y	MARTIN V ET AL: "Involvement of DNA methylation in the control of the expression of an estrogen-induced breast-cancer-associated protein (pS2) in human breast cancers." JOURNAL OF CELLULAR BIOCHEMISTRY. APR 1997, vol. 65, no. 1, April 1997 (1997-04), pages 95-106, XP002324819 ISSN: 0730-2312 abstract page 96, left-hand column, paragraph 2 - right-hand column, paragraph 2 page 97, left-hand column, paragraph 1 page 103, right-hand column, paragraph 2 - page 104, left-hand column, paragraph 2 page 105, left-hand column, paragraph 2 -----	1-4,6-22
Y	RIBIERAS S ET AL: "The pS2/TFF1 trefoil factor, from basic research to clinical applications" BBA - REVIEWS ON CANCER, ELSEVIER SCIENCE BV, AMSTERDAM, NL, vol. 1378, no. 1, 19 August 1998 (1998-08-19), pages F61-F77, XP004281825 ISSN: 0304-419X page F70, right-hand column, paragraph 1 - page F71, right-hand column, paragraph 2 ----- -/--	1-4,6-22

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>TOYOTA MINORU ET AL: "Methylation profiling in acute myeloid leukemia" BLOOD, vol. 97, no. 9, 1 May 2001 (2001-05-01), pages 2823-2829, XP002226261 ISSN: 0006-4971 abstract page 2825, right-hand column, paragraph 2 - page 2826, left-hand column, line 9</p>	4
Y	<p>SCHAUSI DIANE ET AL: "Regulation of the intronic promoter of rat estrogen receptor alpha gene, responsible for truncated estrogen receptor product-1 expression." ENDOCRINOLOGY, JUL 2003, vol. 144, no. 7, July 2003 (2003-07), pages 2845-2855, XP002324924 ISSN: 0013-7227 abstract page 2850, left-hand column, paragraph 2 - page 2852, right-hand column, paragraph 2 page 2853, right-hand column, paragraph 2 - page 2854, left-hand column, paragraph 1</p>	4
A	<p>MARTENS J W M ET AL: "Epigenetic signature predicts failure of endocrine therapy in patients with recurrent breast cancer" BREAST CANCER RESEARCH AND TREATMENT, NIJHOFF, BOSTON, US, vol. 82, no. Supplement 1, 3 June 2003 (2003-06-03), page S72, XP008030522 ISSN: 0167-6806 abstract</p>	1-4,6-22
A	<p>OTTAVIANO Y L ET AL: "METHYLATION OF THE ESTROGEN RECEPTOR GENE CPG ISLAND MARKS LOSS OF ESTROGEN RECEPTOR EXPRESSION IN HUMAN BREAST CANCER CELLS" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 54, no. 10, 15 May 1994 (1994-05-15), pages 2552-2555, XP000999429 ISSN: 0008-5472 page 2552 - page 2555</p> <p style="text-align: center;">----- -/--</p>	1-4,6-22

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>LAPIDUS R G ET AL: "METHYLATION OF ESTROGEN AND PROGESTERONE RECEPTOR GENE 5' CPG ISLANDS CORRELATES WITH LACK OF ESTROGEN AND PROGESTERONE RECEPTOR GENE EXPRESSION IN BREAST TUMORS"</p> <p>CLINICAL CANCER RESEARCH, THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 2, no. 5, May 1996 (1996-05), pages 805-810, XP008030590</p> <p>ISSN: 1078-0432</p> <p>page 805 - page 810</p>	1-4, 6-22

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Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4, 6-22 (as appropriate)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1-4,6-22 (as appropriate)

Methods for characterising a cell proliferative disorder of breast tissues, and/or predicting the metastases free survival, and/or predicting the disease free survival, and/or predicting the response of a subject with said disorder to a treatment comprising one or more treatment which target the estrogen pathway or are involved in estrogen metabolism, production or secretion comprising determining the methylation state of the gene TFF1; an oligonucleotide of at least 18bp derived from the nucleic acid encoding said gene; an oligonucleotide of at least 10bp which hybridises to a nucleic acid encoding said gene; a set of two said oligonucleotides; a kit comprising said oligonucleotides; a method of treatment using said methods.

Inventions 2-58: Claims 1-22 (as appropriate)

Idem as invention 1 but wherein the gene whose methylation state to be determined is:
 Invention 2: EGR4; Invention 3: APC; Invention 4: CDKN2A;
 Invention 5: CSPG2; Invention 6: ERBB2; Invention 7: STMN1;
 Invention 8: STK11; Invention 9: CA9; Invention 10: PAX6;
 Invention 11: SFN; Invention 12: S100A2; Invention 13: TGFBR2; Invention 14: TP53; Invention 15: TP73; Invention 16: PLAU; Invention 17: TMEFF2; Invention 18: ESR1;
 Invention 19: SYK; Invention 20: HSPB1; Invention 21: RASSF1; Invention 22: TES; Invention 23: GRIN2D; Invention 24: PSAT1; Invention 25: CGA; Invention 26: CYP2D6;
 Invention 27: COX7A2L; Invention 28: ESR2; Invention 29: PITX2; Invention 30: VTN; Invention 31: SULT1A1; Invention 32: PCAF; Invention 33: PRKCD; Invention 34: ONECUT2;
 Invention 35: BCL6; Invention 36: WBP11; Invention 37: MX1; Invention 38: APP; Invention 39: ORC4L; Invention 40: METO1;
 Invention 41: TBC1D3; Invention 42: GRB7; Invention 43: CDK6; Invention 44: SEQ ID NO: 47; Invention 45: SEQ ID NO: 48; Invention 46: ABCA8; Invention 47: SEQ ID NO: 50;
 Invention 48: SEQ ID NO: 51; Invention 49: MARK2; Invention 50: ELK1; Invention 51: Q8WUT3; Invention 52: CGB; Invention 53: BSG; Invention 54: BCKDK; Invention 55: SOX8; Invention 56: DAG1; Invention 57: SEMA4B; Invention 58: ESR1 (exon 8).

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box II.1

Claims 1-16 include the step of obtaining a biological sample from a subject and are therefore directed to a diagnostic method practised on the human/animal body. Claim 22 refers to the use of the methods of claims 1-16 for the treatment of breast cell proliferative disorders and is therefore considered to be a method of treatment. Consequently, the search has been carried out and based on the differential methylation state of genes in breast cell proliferative disorders and the detection thereof.

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02059347	A	01-08-2002	US 2003017454 A1	23-01-2003
			WO 02059347 A2	01-08-2002
			US 2003138783 A1	24-07-2003
WO 0238801	A	16-05-2002	WO 0238801 A1	16-05-2002
			AU 1481102 A	21-05-2002
			EP 1337662 A1	27-08-2003
			US 2004086944 A1	06-05-2004